Compounds and Methods for Treating Tumors, Cancer and Hyperproliferative Diseases

Related Applications

This application claims the benefit of priority of provisional application s.n. 60/425,389, filed 11/12/2002, entitled "Molecules for the Inhibition of Cell Proliferation, the entirety of its contents being incorporated by reference herein.

Field of the Invention

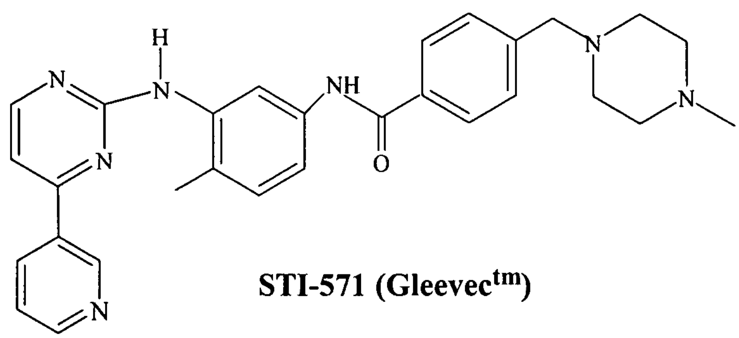
The present invention relates to novel compounds, pharmaceutical compositions and methods for treating tumors, cancer and hyperproliferative diseases including psoriasis, genital warts and hyperproliferative cell growth diseases, including hyperproliferative keratinocyte diseases such as hyperkeratosis, ichthyosis, keratoderma or lichen planus.

The subject matter disclosed in this application was supported, at least in part by grant number NIH/NCI P01 CA49639. As such, the government retains certain rights in the invention.

Background of the Invention

Chronic myelogenous leukaemia (CML) is a hematological stem cell disorder that is associated with a specific chromosomal abnormality whereby the Abelson (*c-abl*) proto-oncogene, translocated from chromosome 9, is fused to the breakpoint cluster region (*bcr*) gene on chromosome 22 as shown in slide 2. The *bcr-abl* fusion gene codes for a tyrosine kinase that is activated constitutively and is thus able to transform cells and cause malignancy: white blood cells divide constantly leading to a blast crisis. Recently, a selective inhibitor of p210-Bcr-Abl tyrosine kinase, STI-571, was designed by Druker and co-workers. See Drucker, et al., *Nature Med.,* **2**, 561-566 (1996) and Schindler, et al., *Science*, **289**, 1938-1941 (2000). STI-571 (tradename: Gleevec®) is the first kinase inhibitor approved by the FDA and blocks the ATP-binding site on Abl and Bcr-Abl kinases, resulting in both inhibition of proliferation and induction of apoptosis in Bcr-Abl

positive cell lines. While STI-571 leads to a complete hematological response in 96% of the patients treated for more than four weeks, patients with advanced disease often relapse, their tumor cells become resistant to the drug and these eventually grow out of control. One of the possible causes of resistance of cancerous cells to STI-571 is a mutation that replaces a single amino acid in the active site of the kinase, preventing binding of the drug to the kinase. See Gorre, et al., *Science*, **293**, 876-880 (2001).



STI-571 (Gleevec^{tm})

The present invention relates to the goal of preparing novel tyrosine kinase inhibitors that would be given alone or in combination with STI-571 to cancer patients since the cancerous cells should be less able to become resistant to all the drugs at once. In addition, novel active substances that would hit alternative targets and work alone or in synergy with STI-571 are also sought after targets.

Objects of the Invention

It is an object of the invention to provide novel compounds which can be used to treat one or more of tumors, cancer and proliferative diseases as otherwise described herein.

It is an additional object of the invention to provide pharmaceutical compounds based upon the compounds disclosed herein.

It is yet another object of the invention to provide methods to treat patients for one or more of tumors, cancer, hyperproliferative diseases including psoriasis, genital warts and hyperproliferative cell growth diseases, including hyperproliferative keratinocyte diseases such as hyperkeratosis, ichthyosis, keratoderma or lichen planus.

It is still another object of the present invention to use the present compounds alone or synergistically with other anti-tumor/anti-cancer agents for the treatment of tumors and/or cancer in patients.

It is yet another object of the present invention to provide pharmaceutical compositions which may be advantageously used in combination with other anti-tumor/anti-cancer agents in the interest of providing synergistic therapy to patients in need of such therapy.

One or more of these and/or other objects of the invention will be readily apparent from a review of the disclosure of the present invention herein.

Brief Description of the Figures

Figure 1 depicts a number of representative compounds according to the present invention.

Figure 2 depicts a chemical scheme directed to certain furan compounds according to the present invention.

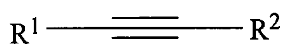
Figure 3 depicts a chemical scheme directed to alternative furan compounds according to the present invention.

Figure 4 shows a simple chemical scheme directed to the synthesis of acetylene compounds according to the present invention.

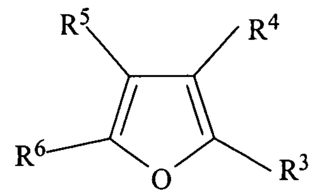
Figures 5-12 show the effect of varying the chemical structure of a number compounds according to the present invention on biological activity.

Summary of the Invention

The present invention relates to compounds according to either of the structures set forth below:



or



where R^1 is H, OH, F, Cl, Br, I, a C_1-C_6 optionally substituted alkyl or alkenyl group, an optionally substituted aryl group or a $\overset{\displaystyle O}{\overset{\|}{C}}$-$R_a$ group;

R_a is a H, OH, C_1-C_{10}, optionally substituted alkyl or alkenyl group, an optionally substituted O-(C_1-C_7 alkyl group) or O-aryl group, an amine group which is optionally substituted with at least one C_1-C_{10} alkyl group which may be optionally substituted, or a single optionally substituted aryl group, biphenyl group, (C_1-C_6) alkylenearyl group, (C_1-C_6) alkylenebiphenyl group, heteroaryl group, heterocyclic group, (C_1-C_6) alkylene heteroaryl group or (C_1-C_6) alkylene heterocyclic group;

R^2 is a $\overset{\displaystyle O}{\overset{\|}{C}}$-$R_b$ group;

R_b is a H, OH, C_1-C_{10}, optionally substituted alkyl or alkenyl group, an optionally substituted O-(C_1-C_7 alkyl group) or O-aryl group, an amine group which is optionally substituted with at least one C_1-C_{10} alkyl group which may be optionally substituted, or a single optionally substituted aryl group, biphenyl group, (C_1-C_6) alkylenearyl group, (C_1-C_6) alkylenebiphenyl group, heteroaryl group, heterocyclic group, (C_1-C_6) alkylene heteroaryl group or (C_1-C_6) alkylene heterocyclic group;

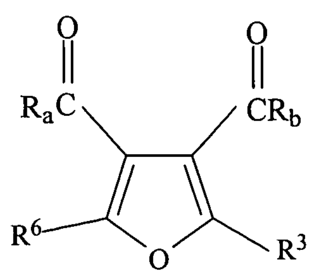
R^3 and R^6 are each independently selected from H, OH, F, Cl, Br, I, a C_1-C_6 optionally substituted alkyl or alkenyl group, an optionally substituted aryl group, a carbamate, alkylene carbamate, urethane or alkylene urethane;

R^4 is a $\overset{\displaystyle O}{\overset{\|}{C}}$-$R_a$ group, wherein R_a is as described above; and

R^5 is a $\overset{\displaystyle O}{\overset{\|}{C}}$-$R_b$ group, wherein R_b is as described above,
with the proviso that at least one of R^1 and R^2 or R^4 and R^5 contains an R_a or R_b group which is an amine group which is optionally substituted with at least one C_1-C_{10} alkyl group which may be optionally substituted, or a single optionally substituted aryl group, biphenyl group, (C_1-C_6) alkylenearyl group, (C_1-C_6) alkylenebiphenyl group, heteroaryl group, heterocyclic group, (C_1-C_6) alkylene heteroaryl group or (C_1-C_6) alkylene heterocyclic group;
or a stereoisomer, pharmaceutically acceptable salt, solvate, and polymorph thereof.

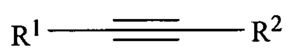
In preferred aspects of the present invention, the compounds according to the present invention contain at least one ester group and at least one amide group, preferably with each such group bonded directly to the acetylene or furan moieties, such that R^1 forms an ester group with the acetylenic group and R^2 forms an amide group with the acetylenic moiety. In the case of the furan compounds, R^4 preferably forms an amide group such that R_b is preferably an amine or substituted amine group and R^5 preferably forms an ester group with the furan moiety, such that R_a is preferably an O-alkyl or O-aryl group as otherwise defined hereinabove. These compounds are presented below.

or



Pharmaceutical compositions based upon the above-described compounds comprise an effective amount of compound in combination with a pharmaceutically acceptable carrier, additive or excipient.

Other aspects of the present invention are directed to methods of treating tumors, cancer, hyperproliferative diseases including psoriasis, genital warts and hyperproliferative cell growth diseases, including hyperproliferative keratinocyte diseases such as hyperkeratosis, ichthyosis, keratoderma or lichen planus, the method comprising administering to a patient in need thereof an effective amount of a compound according to the formula:



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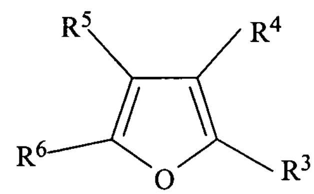


where R^1 is H, F, Cl, Br, I, a C_1-C_6 optionally substituted alkyl or alkenyl group, an optionally substituteded aryl group or a $\overset{\displaystyle O}{\overset{\|}{C}}\text{-}R_a$ group;

R_a is a C_1-C_{10}, optionally substituted alkyl or alkenyl group, an optionally substituted O-(C_1-C_7 alkyl group) or O-aryl group, an amine group which is optionally substituted with at least one C_1-C_{10} alkyl group which may be optionally substituted, or a single optionally substituted aryl group, biphenyl group, (C_1-C_6) alkylenearyl group, (C_1-C_6) alkylenebiphenyl group, heteroaryl group, heterocyclic group, (C_1-C_6) alkylene heteroaryl group or (C_1-C_6) alkylene heterocyclic group;

R^2 is a $\overset{\displaystyle O}{\overset{\|}{C}}\text{-}R_b$ group;

R_b is a C_1-C_{10}, optionally substituted alkyl or alkenyl group, an optionally substituted O-(C_1-C_7 alkyl group) or O-aryl group, an amine group which is optionally substituted with at least one C_1-C_{10} alkyl group which may be optionally substituted, or a single

optionally substituted aryl group, biphenyl group, (C_1-C_6) alkylenearyl group, (C_1-C_6) alkylenebiphenyl group, heteroaryl group, heterocyclic group, (C_1-C_6) alkylene heteroaryl group or (C_1-C_6) alkylene heterocyclic group;

R^3 and R^6 are each independently selected from H, F, Cl, Br, I, a C_1-C_6 optionally substituted alkyl or alkenyl group, an optionally substituteded aryl group, a carbamate, alkylene carbamate, urethane or alkylene urethane;

R^4 is a $\overset{\overset{\displaystyle O}{\|}}{C}\text{-}R_b$ group, wherein R_b is as described above, and

R^5 is a $\overset{\overset{\displaystyle O}{\|}}{C}\text{-}R_a$ group, wherein R_a is as described above;
with the proviso that at least one of R^1 and R^2 or R^4 and R^5 contains an R_a or R_b group which is an amine group which is optionally substituted with at least one C_1-C_{10} alkyl group which may be optionally substituted, or a single optionally substituted aryl group, biphenyl group, (C_1-C_6) alkylenearyl group, (C_1-C_6) alkylenebiphenyl group, heteroaryl group, heterocyclic group, (C_1-C_6) alkylene heteroaryl group or (C_1-C_6) alkylene heterocyclic group;
or a stereoisomer, pharmaceutically acceptable salt, solvate, and polymorph thereof in combination with a pharmaceutically acceptable carrier, additive or excipient.

Detailed Description of the Invention

The following terms are used throughout the specification to describe the present invention:

"Patient" or "subject" is used throughout the specification to describe an animal, generally a mammalian animal, including a human, to whom treatment or use with the compounds or compositions according to the present invention is provided. For treatment or use with/or of those conditions or disease states which are specific for a specific

animal (especially, for example, a human subject or patient), the term patient or subject refers to that particular animal.

"Alkyl" refers to a fully saturated monovalent hydrocarbon radical containing carbon and hydrogen which may be a straight chain, branched, or cyclic group. Examples of alkyl groups are methyl, ethyl, n-butyl, n-heptyl, isopropyl, 2-methylpropyl, cyclopropyl, cyclopropylmethyl, cyclobutyl, cyclopentyl, cyclopentylethyl and cyclohexyl. "Cycloalkyl" groups refer to cyclic alkyl groups such as cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl. C_1-C_7 alkyl groups are preferably used in certain aspects of the present invention, although the alkyl group may be larger, in certain advantageous instances. The term alkyl also refers to monocyclic, bicyclic, tricyclic and tetracyclic alkyl (ie., hydrocarbon) groups. Alkyl groups according to the present invention may be substituted or unsubstituted.

The term "alkenyl" refers to an alkyl group with at least one double bond between adjacent carbon atoms within the chemical group. The term "alkylene" refers to an optionally substituted group having the general formula $-(CH_2)_n-$ where n is a positive integer from 1 to 12, preferably from 1 to 6, more preferably from 1 to 3.

The term "substituted" refers to a chemical group or moiety which occurs on (is bonded to) another group and may include one or more functional groups such an alkyl containing from 1 to 6 carbon atoms, preferably a lower alkyl containing 1-3 carbon atoms, aryl, substituted aryl, acyl, ester, halogen (i.e., alkyl halos, e.g., CF_3), hydroxy, alkoxy, carboxy, alkoxyalkyl, amino, alkyl and dialkyl amino, acylamino, acyloxy, aryloxy, aryloxyalkyl, carboxyalkyl, carboxamido, thio, thioethers, both saturated and unsaturated cyclic hydrocarbons, heterocycles and the like. Alkyl and ester groups, for example, $-\overset{\overset{\displaystyle O}{\|}}{C}-O(C_1-C_6)$alkyl groups are preferred substituents in certain aspects of the present invention. Substituted, for example, as in "substituted alkyl" or "substituted alkenyl", means that in the hydrocarbyl, hydrocarbylene, alkyl, alkenyl or other moiety, at least one hydrogen atom bound to a carbon atom is replaced with one or

more substituents that are functional groups such as hydroxyl, alkoxy, thio, amino, halo, and the like, as described above. When the term "substituted" appears prior to a list of possible substituted groups, it is intended that the term apply to every member of that group.

The term "aryl" refers to a substituted or unsubstituted monovalent aromatic radical having a single ring (e.g., phenyl) or multiple condensed rings (e.g., naphthyl). Other examples include heterocyclic aromatic ring groups having one or more nitrogen, oxygen, or sulfur atoms in the ring, such as imidazolyl, furyl, pyrrolyl, pyridyl, thienyl and indolyl. The term "heteroaryl" refers to an aryl group which contains at least one atom selected from O, N and S.

"Halo" and "halogen" are used in the conventional sense to refer to a chloro, bromo, fluoro or iodo substituent. The terms "haloalkyl," "haloalkenyl" or "haloalkynyl" (or "halogenated alkyl," "halogenated alkenyl," or "halogenated alkynyl") refers to an alkyl, alkenyl or alkynyl group, respectively, in which at least one of the hydrogen atoms in the group has been replaced with a halogen atom.

"Heterocycle" or "heterocyclic" refers to a carbocylic ring wherein one or more carbon atoms have been replaced with one or more heteroatoms such as nitrogen, oxygen or sulfur. A substitutable nitrogen on an aromatic or non-aromatic heterocyclic ring may be optionally substituted. The heteroatoms N or S may also exist in oxidized form such as NO, SO and SO_2. Examples of heterocycles include, but are not limited to, piperidine, pyrrolidine, morpholine, thiomorpholine, piperazine, tetrahydrofuran, tetrahydropyran, 2-pyrrolidinone, δ-velerolactam, δ-velerolactone and 2-ketopiperazine, among numerous others.

The term "biphenyl" refers to a group which contains two optionally substituted aryl groups, preferablyl phenyl groups, which are linked together at a single carbon atom on each phenyl group.

The terms “carbamate”, “alkylene carbamate”, “urethane” or “alkylene urethane” refers to a substituent or moiety which may be represented by the structure $RX\text{-}\overset{O}{\overset{\|}{C}}\text{-}\overset{H}{\overset{|}{N}}\text{-}(CH_2)_y\text{-}$ where R is a optionally substituted C_1-C_8 alkyl group or an aryl group, X is O (carbamate) or N (urethane) and y is from 0 to 6. Compounds according to the present invention based upon a furan skeleton may contain carbamates, alkylene carbamates, urethanes or alkylene urethanes as indicated at R^3 and R^6 of the furan ring.

The term “compound” is used herein to refer to any specific chemical compound disclosed herein. Within its use in context, the term generally refers to a single compound, but in certain instances may also refer to stereoisomers and/or optical isomers (including racemic mixtures) of disclosed compounds.

The term "effective amount" refers to the amount of a selected compound according to the present invention which is used in an amount to produce an intended effect within the context of its use and in particular, the treatment method to be used. The precise amount of a compound according to the present invention used in a given context will vary depending upon the particular compound selected and its intended use, the disease or condition to be treated, the method of delivery, the age and weight of the subject, route of administration, and so forth, but may be easily determined by routine experimentation. In the case of the treatment of a condition or disease state, an effective amount is that amount which is used to effectively treat the particular condition or disease state.

The term "pharmaceutically acceptable” refers to a carrier, additive or excipient which is not unacceptably toxic to the subject to which it is administered.

The term "neoplasia" or “cancer” is used throughout the specification to refer to the pathological process that results in the formation and growth of a cancerous or

malignant neoplasm, i.e., abnormal tissue that grows by cellular proliferation, often more rapidly than normal and continues to grow after the stimuli that initiated the new growth cease. Malignant neoplasms show partial or complete lack of structural organization and functional coordination with the normal tissue and most invade surrounding tissues, metastasize to several sites, and are likely to recur after attempted removal and to cause the death of the patient unless adequately treated. As used herein, the term neoplasia is used to describe all cancerous disease states and embraces or encompasses the pathological process associated with malignant hematogenous, ascitic and solid tumors. Representative cancers include, for example, stomach, colon, rectal, liver, pancreatic, lung, breast, cervix uteri, corpus uteri, ovary, prostate, testis, bladder, renal, brain/CNS, head and neck, throat, Hodgkin's disease, non-Hodgkin's lymphoma, multiple myeloma, leukemia, melanoma, acute lymphocytic leukemia, acute myelogenous leukemia, Ewing's sarcoma, small cell lung cancer, choriocarcinoma, rhabdomyosarcoma, Wilms' tumor, neuroblastoma, hairy cell leukemia, mouth/pharynx, oesophagus, larynx, kidney cancer and lymphoma, among others, which may be treated by one or more compounds according to the present invention.

The term "tumor" is used to describe a malignant or benign growth or tumefacent.

The term "hyperproliferative disease state" refers to a disease state in which cells are growing in an uncontrolled manner, whether that growth is cancerous or not. Such a disease state may be reflected in psoriasis or genital warts or other hyperproliferative cell growth diseases, including hyperproliferative keratinocyte diseases including hyperkeratosis, ichthyosis, keratoderma or lichen planus, all of which disease states may be treated using compounds according to the present invention.

The present invention includes the compositions comprising the pharmaceutically acceptable acid addition salts of compounds of the present invention. The acids which are used to prepare the pharmaceutically acceptable acid addition salts of the aforementioned base compounds useful in this invention are those which form non-toxic acid addition salts, i.e., salts containing pharmacologically acceptable anions, such as the

hydrochloride, hydrobromide, hydroiodide, nitrate, sulfate, bisulfate, phosphate, acid phosphate, acetate, lactate, citrate, acid citrate, tartrate, bitartrate, succinate, maleate, fumarate, gluconate, saccharate, benzoate, methanesulfonate, ethanesulfonate, benzenesulfonate, p-toluenesulfonate and pamoate [i.e., 1,1'-methylene-bis-(2-hydroxy-3 naphthoate)]salts, among others.

The invention also includes compositions comprising base addition salts of the present compounds. The chemical bases that may be used as reagents to prepare pharmaceutically acceptable base salts of the present compounds that are acidic in nature are those that form non-toxic base salts with such compounds. Such non-toxic base salts include, but are not limited to those derived from such pharmacologically acceptable cations such as alkali metal cations (eg., potassium and sodium) and alkaline earth metal cations (e, calcium and magnesium), ammonium or water-soluble amine addition salts such as N-methylglucamine-(meglumine), and the lower alkanolammonium and other base salts of pharmaceutically acceptable organic amines, among others.

The compounds of this invention include all stereoisomers where relevant (i.e, cis and trans isomers) and all optical isomers of the present compounds (eg., R and S enantiomers), as well as racemic, diastereomeric and other mixtures of such isomers, as well as all polymorphs of the compounds.

The compositions of the present invention may be formulated in a conventional manner using one or more pharmaceutically acceptable carriers and may also be administered in controlled-release formulations. Pharmaceutically acceptable carriers that may be used in these pharmaceutical compositions include, but are not limited to, ion exchangers, alumina, aluminum stearate, lecithin, serum proteins, such as human serum albumin, buffer substances such as phosphates, glycine, sorbic acid, potassium sorbate, partial glyceride mixtures of saturated vegetable fatty acids, water, salts or electrolytes, such as prolamine sulfate, disodium hydrogen phosphate, potassium hydrogen phosphate, sodium chloride, zinc salts, colloidal silica, magnesium trisilicate, polyvinyl pyrrolidone, cellulose-based substances, polyethylene glycol, sodium carboxymethylcellulose,

polyacrylates, waxes, polyethylene-polyoxypropylene-block polymers, polyethylene glycol and wool fat.

The compositions of the present invention may be administered orally, parenterally, by inhalation spray, topically, rectally, nasally, buccally, vaginally or via an implanted reservoir. The term "parenteral" as used herein includes subcutaneous, intravenous, intramuscular, intra-articular, intra-synovial, intrasternal, intrathecal, intrahepatic, intralesional and intracranial injection or infusion techniques. Preferably, the compositions are administered orally, intraperitoneally or intravenously.

Sterile injectable forms of the compositions of this invention may be aqueous or oleaginous suspension. These suspensions may be formulated according to techniques known in the art using suitable dispersing or wetting agents and suspending agents. The sterile injectable preparation may also be a sterile injectable solution or suspension in a non-toxic parenterally-acceptable diluent or solvent, for example as a solution in 1, 3-butanediol. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose, any bland fixed oil may be employed including synthetic mono- or di-glycerides. Fatty acids, such as oleic acid and its glyceride derivatives are useful in the preparation of injectables, as are natural pharmaceutically-acceptable oils, such as olive oil or castor oil, especially in their polyoxyethylated versions. These oil solutions or suspensions may also contain a long-chain alcohol diluent or dispersant, such as Ph. Helv or similar alcohol.

The pharmaceutical compositions of this invention may be orally administered in any orally acceptable dosage form including, but not limited to, capsules, tablets, aqueous suspensions or solutions. In the case of tablets for oral use, carriers which are commonly used include lactose and corn starch. Lubricating agents, such as magnesium stearate, are also typically added. For oral administration in a capsule form, useful diluents include lactose and dried corn starch. When aqueous suspensions are required for oral use, the active ingredient is combined with emulsifying and suspending agents. If desired, certain

sweetening, flavoring or coloring agents may also be added.

Alternatively, the pharmaceutical compositions of this invention may be administered in the form of suppositories for rectal administration. These can be prepared by mixing the agent with a suitable non-irritating excipient which is solid at room temperature but liquid at rectal temperature and therefore will melt in the rectum to release the drug. Such materials include cocoa butter, beeswax and polyethylene glycols.

The pharmaceutical compositions of this invention may also be administered topically, especially to treat skin cancers, psoriasis or other diseases which occur in or on the skin. Suitable topical formulations are readily prepared for each of these areas or organs. Topical application for the lower intestinal tract can be effected in a rectal suppository formulation (see above) or in a suitable enema formulation. Topically-acceptable transdermal patches may also be used.

For topical applications, the pharmaceutical compositions may be formulated in a suitable ointment containing the active component suspended or dissolved in one or more carriers. Carriers for topical administration of the compounds of this invention include, but are not limited to, mineral oil, liquid petrolatum, white petrolatum, propylene glycol, polyoxyethylene, polyoxypropylene compound, emulsifying wax and water. Alternatively, the pharmaceutical compositions can be formulated in a suitable lotion or cream containing the active components suspended or dissolved in one or more pharmaceutically acceptable carriers. Suitable carriers include, but are not limited to, mineral oil, sorbitan monostearate, polysorbate 60, cetyl esters wax, cetearyl alcohol, 2-octyldodecanol, benzyl alcohol and water.

For ophthalmic use, the pharmaceutical compositions may be formulated as micronized suspensions in isotonic, pH adjusted sterile saline, or, preferably, as solutions in isotonic, pH adjusted sterile saline, either with our without a preservative such as benzylalkonium chloride. Alternatively, for ophthalmic uses, the pharmaceutical

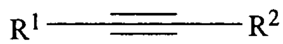
compositions may be formulated in an ointment such as petrolatum.

The pharmaceutical compositions of this invention may also be administered by nasal aerosol or inhalation. Such compositions are prepared according to techniques well-known in the art of pharmaceutical formulation and may be prepared as solutions in saline, employing benzyl alcohol or other suitable preservatives, absorption promoters to enhance bioavailability, fluorocarbons, and/or other conventional solubilizing or dispersing agents.

The amount of compound in a pharmaceutical composition of the instant invention that may be combined with the carrier materials to produce a single dosage form will vary depending upon the host and disease treated, the particular mode of administration. Preferably, the compositions should be formulated to contain between about 0.5 milligram to about 750 milligrams, more preferably about 1 milligram to about 600 milligrams, and even more preferably about 10 milligrams to about 500 milligrams of active ingredient.

It should also be understood that a specific dosage and treatment regimen for any particular patient will depend upon a variety of factors, including the activity of the specific compound employed, the age, body weight, general health, sex, diet, time of administration, rate of excretion, drug combination, and the judgment of the treating physician and the severity of the particular disease or condition being treated.

Other aspects of the present invention are directed to methods of treating tumors, cancer, hyperproliferative diseases including psoriasis, genital warts and hyperproliferative cell growth diseases, including hyperproliferative keratinocyte diseases such as hyperkeratosis, ichthyosis, keratoderma or lichen planus, the method comprising administering to a patient in need thereof an effective amount of a compound according to the formula:



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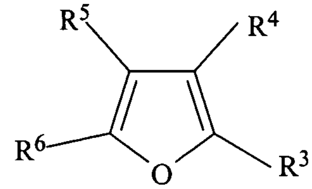


where R^1 is H, OH, F, Cl, Br, I, a C_1-C_6 optionally substituted alkyl or alkenyl group, an optionally substituted aryl group or a $\overset{O}{\overset{\|}{C}}$-$R_a$ group;

R_a is a H, OH, C_1-C_{10}, optionally substituted alkyl or alkenyl group, an optionally substituted O-(C_1-C_7 alkyl group) or O-aryl group, an amine group which is optionally substituted with at least one C_1-C_{10} alkyl group which may be optionally substituted, or a single optionally substituted aryl group, biphenyl group, (C_1-C_6) alkylenearyl group, (C_1-C_6) alkylenebiphenyl group, heteroaryl group, heterocyclic group, (C_1-C_6) alkylene heteroaryl group or (C_1-C_6) alkylene heterocyclic group;

R^2 is a $\overset{O}{\overset{\|}{C}}$-$R_b$ group;

R_b is a H, OH, C_1-C_{10}, optionally substituted alkyl or alkenyl group, an optionally substituted O-(C_1-C_7 alkyl group) or O-aryl group, an amine group which is optionally substituted with at least one C_1-C_{10} alkyl group which may be optionally substituted, or a single optionally substituted aryl group, biphenyl group, (C_1-C_6) alkylenearyl group, (C_1-C_6) alkylenebiphenyl group, heteroaryl group, heterocyclic group, (C_1-C_6) alkylene heteroaryl group or (C_1-C_6) alkylene heterocyclic group;

R^3 and R^6 are each independently selected from H, OH, F, Cl, Br, I, a C_1-C_6 optionally substituted alkyl or alkenyl group, or an optionally substituteded aryl group;

R^4 is a $\overset{O}{\overset{\|}{C}}$-$R_a$ group, wherein R_b is as described above; and

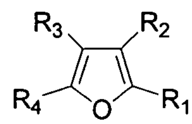
R^5 is a $\overset{\displaystyle O}{\overset{\|}{C}}\text{-}R_b$ group, wherein R_b is as described above,
with the proviso that at least one of R^1 and R^2 or R^4 and R^5 contains an R_a or R_b group which is an amine group which is optionally substituted with at least one C_1-C_{10} alkyl group which may be optionally substituted, or a single optionally substituted aryl group, biphenyl group, (C_1-C_6) alkylenearyl group, (C_1-C_6) alkylenebiphenyl group, heteroaryl group, heterocyclic group, (C_1-C_6) alkylene heteroaryl group or (C_1-C_6) alkylene heterocyclic group;
or a stereoisomer, pharmaceutically acceptable salt, solvate, and polymorph thereof, optionally in combination with a pharmaceutically acceptable additive, carrier or excipient.

Representative compounds of the present invention can be readily synthesized in accordance with the general synthetic methods described below and are illustrated more particularly in the schemes that follow. Since the schemes are illustrative, the invention should not be construed as being limited by the chemical reactions and conditions expressed. The preparation of the various starting materials used in the schemes is well within the skill of persons versed in the art. Compounds not specifically mentioned may be readily synthesized by analogy following techniques and methods well known to those of skill in the art.

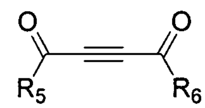
Unless specified to the contrary, reactions herein occur at approximately atmospheric pressure and at a temperature of between about 0° C and the boiling point of any organic solvent used in the reaction. Inert organic solvents such as dichloromethane, diethyl ether, dimethylformamide, chloroform or tetrahydrofuran are preferred solvents in the reactions disclosed herein, although other solvents may be used where appropriate or indicated. Reaction times can range from about one hour to about forty-eight hours, and reactants optionally are stirred, shaken, or agitated. Reactions can be done in one pot or in steps, unless specified to the contrary.

General Chemistry and Structure Activity

Two scaffolds described hereafter preferably have been used: a planar scaffold, represented by compounds containing a furan core with various groups displayed at C-2, C-3, C-4 and C-5 of the furan and an acetylene core (structure index).



Furan core



Acetylene core

Some furans (R1= H or CH_3, R2= CONHCy or CO_2CH_3, R3= CO_2CH_3 or CONHCy, R4= CH_3 or H) were prepared by Diels-Alder cycloaddition of an acetylene bearing an amide and an ester group (R5 and R6) on each side of the triple bond, followed by regioselective reduction of the unsubstituted double bond and retro Diels-Alder reaction (Figure 2). The other furans (R1= H, R2= CONHCy, R3= CO_2CH_3, R4= $CH_2CH_2CH_2NHCO_2R$ with R=CH_3, $(CH_2)_3CH_3$, $CH_2CH(CH_2CH_3)_2$, $CH_2CH(NHBoc)CH(CH_3)_2$, CH_2Cy, CH_2Ph) were prepared from pyrrolidinone after conversion to its corresponding imide, diazotransfer, deacylation, cycloaddition with an acetylene bearing an amide and an ester groups on each side of the triple bond, cycloreversion and heating with an alcohol (Figure 3).

The acetylenes were prepared by deprotonation of a propiolate (either methyl or *tert*-butyl) with *n*-butyllithium and subsequent reaction with an isocyanate (Figure 4). Modifications may be readily made following the aforementioned schemes. The furan and acetylene libraries were both tested for activity in a cell-based assay where the death of engineered murine myeloid cells (32D-bcr-abl), the survival of which depends on the activity of bcr-abl tyrosine kinase, was sought. The control cell line that enables the determination of the selectivity of the compounds is also a murine cell line, which does not depend on bcr-abl kinase activity to survive.

The biological activity of these compounds was evaluated in two ways, a murine cell line differential proliferation assay and a NCI 60 human carcinoma cell-line growth

inhibition and cell death assay. The murine cell death assays were performed using a p210bcrabl transformed 32D murine cell line. This is a differential assay, measuring the ability of the molecule to selectively inhibit the transformed cells (32Dbcrabl) over the non-transformed, growth factor dependent parental cell line (32D). The NCI assay was performed in the Developmental Therapeutics Program at the National Cancer Institute. This assay measures the inhibition of cell growth and cell death from sixty different human carcinomas. Both the acetylene and furan structural cores represent novel chemical entities with no prior reports of biological activity. Biological data collected thus far show that both the ester and amide moiety provide the greatest activity and are preferred. In addition, subtle changes in R1 confer major differences in biological activity, suggesting a specific cellular target for these molecules. The molecules K1P, AC19, AC22, AN7A and AN7B (Figure 1) showed good activity against a number of carcinoma and model carcinoma cell lines. At present, the use of these compounds is to be preferred in the treatment of tumors and cancer.

Biological and Structure Activity

The furan and acetylene libraries were both tested for activity in a cell-based assay where the death of engineered murine myeloid cells (32D-bcr-abl), the survival of which is depends on the activity of bcr-abl tyrosine kinase, was sought. The control cell line that enables the determination of the selectivity of the compounds is also a murine cell line, which does not depend on bcr-abl kinase activity to survive.

We have found that a carbonyl on either side of the triple bond was clearly preferred for activity since compounds AC2, AC4, AC5 and AC11 showed little or no activity (see structure index in Figure 1). Investigation of the importance of the ester on activity, compounds K1P and AC1 were compared. As seen in Figure 5, the two compounds performed equally well in the assay in terms of activity and selectivity. At 100nM, the compounds are still active with 50% of leukemic cells surviving and 100% of the control cells surviving. The optimization was therefore continued at the amide site. The ester can be later modified to improve the pharmacokinetic properties of the future drug. Investigation of the scaffold right side was then carried out as shown in Figure 6. Changing the amide group from cyclohexylamide (K1P) to

phenylamide (AC6) increased both selectivity and activity while adding an electron donating group at the para position of the aromatic ring (AC3) decreased activity and selectivity dramatically. The position of substitution on the ring was further tested with compounds AC15, AC16, and AC17. It was found that activity was regained at the 1uM level in the case of the ortho, meta and di-meta substitution while selectivity remained low (Figure 7). Figure 8 shows the effect of the nature of the substituent on the phenyl ring and revealed that two electron withdrawing groups such as fluorine at the ortho position (AC9) rendered the molecule inactive while two bulky inductive group such as isopropyl groups (AC10) had moderate activity but no selectivity. Adding an extra methylene unit between the phenyl ring and the amide nitrogen gave an active benzylamide compound (AC13) with little selectivity. These cell assays were usually carried out using 50 cell/well in average and Figure 8 shows the result of an assay that used a varying number of cells per well, while keeping the concentration of the compound constant at 1uM. Complete selectivity and activity was observed at 2000 cells per well. Using the phenylamide (AC6) as a lead, acetylenes AC19, AC21 and AC22 were designed and prepared to explore the space available for binding on the amide side. As seen Figure 9, these 3 new compounds all exhibit excellent activity at 100 nM but only AC19 shows selectivity. Next a combination of STI-571 and compounds AC22 and AC19 was tested. Figure 10 shows that STI-571 is moderately active (30% of the myeloid engineered murine cells are killed but the all the control cells are still alive) and selective at 10 nM in our assay while AC22 is very active but not selective at 100 nM and not active at 10nM. As a combination, however, AC22 and STI-571 show complete activity and 70% selectivity, while at 10 nM the activity remains and the selectivity is enhanced to 100%. Neither of these compounds, on its own, displays such activity and selectivity, therefore it seems that a combination of AC22 and STI-571 act in synergy to combat leukemic cells while being non toxic to control cells. A different result is obtained with AC19, which, in combination with STI-571 does not increase the activity or selectivity compared to STI-571 alone. This suggests that AC19 and STI-571 might be acting with the same target while AC22 and STI-571 might bind to different sites thereby showing a multiplicative effect of either compound (Figure 11).

Furans AN7A and AN7B were also evaluated for activity and selectivity in our assay and showed incredible activity and selectivity (both 100% at 10 nM); the graph

shown in Figure 12 corresponds to the cell assay results for furan AN7B. In order to obtain additional information about the behavior of our compounds in cancerous cells, 18 compounds were submitted to and accepted by the NCI for testing on 60 human carcinoma cell lines as set forth in the examples section. This would confirm the activity seen in our cell-based assay and maybe give an insight into the mechanism of action and biological target of the acetylene/furan compounds. While the results were somewhat disappointing (AC19 did not show activity below 10uM and AC22 showed mediocre growth inhibition between 2.6 and 7.3 uM in leukemia cell lines only), K1P had an interesting pattern of activity whereby it inhibited growth of leukemia cell lines (GI50 between 0.8 and 5uM) and renal cell lines (GI50: 2.5uM to 2.7uM). As a result, K1P was singled out by the NCI for further testing: MTD (Maximum Tolerated Dose) and murine hollow fiber *in vivo* assay. These are being carried out at the present time, along with testing of furans AN7A and AN7B in the 60 human cancer cell lines.

The invention is described further in the following examples, which are illustrative and in no way limiting.

EXAMPLES

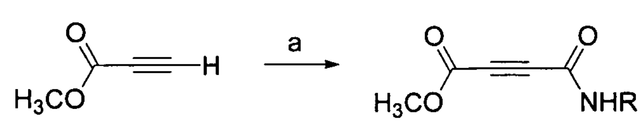
In order to access a representative range of compounds using commercially available starting materials, the general strategy for the preparation of the acetylenes involved the deprotonation of methyl propiolate with *n*-butyllithium (1.6M in hexanes) at –78 °C followed by addition of the desired isocyanate, source of the diversity at the amide moiety. It was found that the use of 1.05 eq of *n*-Buli gave a cleaner product than the use of 1.5eq. Also, for compounds of preparation type 2 (from AC14 onwards), it was found that stirring for a reduced amount of time increased the yield.

The final compounds were obtained in moderate to high yields (23-84%). Purification of these compounds was found difficult; they were generally purified by careful column chromatography followed by recrystallisation. In some case, HPLC purification was also required.

General experimental conditions

^{1}H- and ^{13}C- nuclear magnetic spectra (NMR) were recorded as solutions in deuteriated chloroform ($CDCl_3$) unless stated otherwise with tetramethylsilane as the internal reference, on a DPX-400 MHz or 500 MHz Brucker Avance FT-NMR spectrometer. Chemical shift values (δ) are given in part per million (ppm) and coupling constants (*J*) are expressed in Hertz (Hz). Mass spectra were recorded at the UIUC School of chemical Science and were obtained by electron ionisation (EI) technique. Elemental analyses were performed by Atlantic Microlab, Inc. Routine analytical thin layer chromatography (TLC) was carried out on J. T. Baker Si250 F_{254} glass-backed plates. The plates were developed with the appropriate solvent system and visualized either by UV lamp or dipping into Hanessian stain and heating with a heat gun. Column chromatography was carried out using 230-400 mesh, 60 A, silica gel from Silicycle. Reagents were obtained from Aldrich, Sigma or Fluka. High performance liquid chromatography was performed on a Varian Chrompack Microsorb-MV 100-5 C-18 column (250 × 4.6 × ¼'' mm) using Varian Prostar 210-SDM pumps with an isocratic mixture of methanol and water (80:20); UV detection was at 254 nm with a Varian Prostar 320-UV/VIS detector. Solvents were Analar grade except for THF, which was puriss grade ($H_2O \leq 0.005$ %) and used without further purification. When mixed solvent systems were used, the ratios are v/v. When ethyl acetate and hexanes are used as a mixture, the percentage given is in ethyl acetate (i. e. ethyl acetate-hexanes 5%).

Type 1 procedure for the preparation of acetylenes

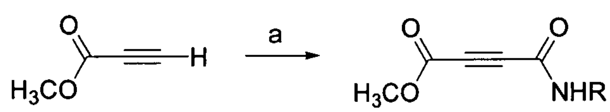


(a) i) *n*-BuLi (1.6M in hexanes, 1.05 eq), THF, -78°C, 40 min;
ii) RNCO (1.3 eq), THF, -78°C, 4 h.

A solution of methyl propiolate (0.445 ml, 5 mmol) in dry THF (25 ml) was cooled to -78°C under N_2, before a solution of *n*-butyllithium (1.6M in hexanes, 3.3 ml,

5.25 mmol) was added dropwise. The mixture was stirred at that temperature for 40 min before the isocyanate (6.5 mmol) was added dropwise. The resulting reaction mixture was allowed to stir at -78 °C for 4 h. Trimethylsilyl chloride (2ml) was added and the mixture was stirred for a further 30 min prior to addition of aqueous hydrochloric acid (1N, 6.5 ml) and the reaction mixture was allowed to warm to room temperature. The resulting two phases were separated and the aqueous layer was extracted with ethyl acetate (3 x 20 ml). The combined organic extracts were dried over sodium sulfate, filtered and concentrated *in vacuo* to give an oil which was purified by column chromatography.

Type 2 procedure for the preparation of acetylenes

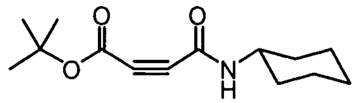


(a) i) *n*-BuLi (1.6M in hexanes, 1.05 eq), THF, -78°C, 30 min;
ii) RNCO (1.1 eq), THF, -78°C, 40 min.

A solution of methyl propiolate (0.445 ml, 5 mmol) in dry THF (25 ml) was cooled to -78°C under N_2, before a solution of *n*-butyllithium (1.6M in hexanes, 3.3 ml, 5.25 mmol) was added dropwise. The mixture was stirred at that temperature for 30 min before the isocyanate (5 mmol) was added dropwise. The resulting reaction mixture was allowed to stir at -78 °C for 30 min. A saturated aqueous solution of ammonium chloride (20 ml) was added and the mixture was allowed to warm to room temperature. The resulting two phases were separated and the aqueous layer was extracted with ethyl acetate (3 x 20 ml). The combined organic extracts were washed with saturated aqueous sodium hydrogen carbonate (20 ml), dried over magnesium sulfate, filtered and concentrated *in vacuo* to give an oil which was purified by column chromatography. The resulting crystalline compounds were recrystallised from hexanes and ethyl acetate.

Characterization of compounds used for comparison:

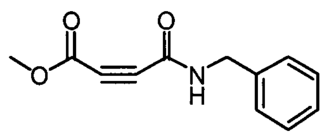
AC1



AC1

76 % yield; R_f 0.3 (hex/EA 4:1); (Found C, 66.82; H, 8.49; N, 5.60; O, 19.04; $C_{14}H_{21}NO_3$ requires C, 66.91; H, 8.42; N, 5.57; O, 19.10); (retention time minutes, seconds); ^{1}H-NMR (400 MHz, $CDCl_3$) 5.66 (1H, br s), 3.85-3.81 (1H, m), 1.93 (2H, dd, *J* 12.6, 3.5), 1.71-1.70 (2H, m), 1.54 (1H, m), 1.50 (9H, s), 1.37-1.35 (2H, m) and 1.18-1.15 (3H, m); ^{13}C-NMR (100 MHz, $CDCl_3$) 151.3 (C_q), 150.1 (C_q), 85.1 (C_q), 75.4 (C_q), 74.8 (C_q), 49.1 (CH), 32.6 (2 x CH_2), 27.9 (3 x CH_3), 24.9 (CH_2) and 24.6 (CH_2); *m/z* (EI) 251.152206 (M^+, $C_{14}H_{21}NO_3$ requires 251.152144), 251 (M^+, 5 %), 152 (MH^+-$CO_2{}^t$Bu, 47), 114 (100), 98 (12) and 83 (30).

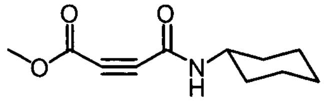
AC13



AC13

48 % yield; **R_f (hex/EA,)**; (Found C, 66.24; H, 5.04; N, 6.44; O, 21.98; $C_{12}H_{11}NO_3$ requires C, 66.35; H, 5.10; N, 6.45; O, 22.10); (retention time 3 minutes, 57 seconds); ^{1}H-NMR (400 MHz, $CDCl_3$) 7.38-7.27 (5H, m), 6.2 (1H, br s), 4.62 (2H, d, *J* 5.9) and 3.82 (3H, s); ^{13}C-NMR (100 MHz, $CDCl_3$) 152.6 (C_q), 150.5 (C_q), 136.4 (C_q), 129.0, 128.2, 128.0 and 127.3 (5 x CH), 77.2 (C_q), 73.9 (C_q), 53.4 (CH_3) and 44.1 (CH_2); *m/z* (EI) 217.074208 (M^+, $C_{12}H_{11}NO_3$ requires 217.073893), 217 (M^+, 23 %), 159 (MH^+-CO_2Me, 68) and 106 ($PhNH^+$, 100).

K1P

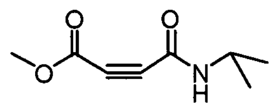


K1P

66% yield; R_f 0.15 (hex/EA, 4:1); (Found C, 63.12; H, 7.13; N, 6.64; O, 23.07; $C_{11}H_{15}NO_3$ requires C, 63.14; H, 7.22; N, 6.70; O, 22.94); (retention time 2 minutes, 56 seconds); ^{1}H-NMR (500 MHz, $CDCl_3$) 5.98 (1H, br s), 3.86-3.84 (1H, m), 3.83 (3H, s),

1.95-1.92 (2H, m), 1.74-1.70 (2H, m), 1.61-1.57 (1H, m), 1.37-1.35 (2H, m) and 1.19-1.17 (2H,m); ^{13}C-NMR (125 MHz, $CDCl_3$) 152.8 (C_q), 149.7 (C_q), 77.9 (C_q), 73.2 (C_q), 53.3 (CH_3), 49.3 (CH), 32.6, 25.3 and 24.6 (5 x CH_2); *m/z* (EI) 209.1045986 (M^+, $C_{11}H_{15}NO_3$ requires 209.105194), 209 (M^+, 6 %), 166 (44) and 128 (100).

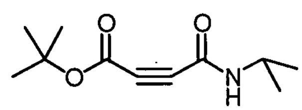
K11P



K11P

68% yield; R_f 0.16 (hex/EA, 4:1); (Found C, 56.59; H, 6.53; N, 8.16; O, 28.64; $C_8H_{11}NO_3$ requires C, 56.80;H, 6.55; N, 8.28; O, 28.37); (retention time 3 minutes, 5 seconds); ^{1}H-NMR (400 MHz, $CDCl_3$) 5.84 (1H, br s), 4.18-4.07 (1H, m), 3.83 (3H, s) and 1.20 (6H, d, *J* 6.5); ^{13}C-NMR (100 MHz, $CDCl_3$) 152.8 (C_q), 149.7 (C_q), 77.7 (C_q), 73.1 (C_q), 53.4 (CH_3), 45.5 (CH) and 22.3 (2 x CH_3); *m/z* (EI) 169.073537(M^+, $C_8H_{11}NO_3$ requires 169.073893), 169 (M^+, 17 %), 154 (M^+-Me, 100), 138 (M^+-OMe, 16) and 111 (MH^+-CO_2Me, 61).

K18P

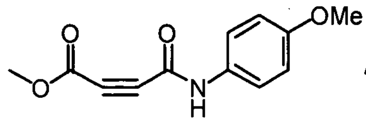


K18P

84% yield; **Rf (hex/EA,);** (Found C, 65.59; H, 8.12; N, 6.66; O, 22.93; $C_{11}H_{17}NO_3$ requires C, 62.54; H, 8.11; N, 6.63; O, 22.72); (retention time 3 minutes, 39 seconds); ^{1}H-NMR (400 MHz, $CDCl_3$) 5.77 (1H, br s), 4.17-4.07 (1H, m), 1.50 (9H, s) and 1.19 (6H, d, *J* 6.5); ^{13}C-NMR (100 MHz, $CDCl_3$) 151.2 (C_q), 150.2 (C_q), 85.1 (C_q), 75.3 (C_q), 74.7 (C_q), 42.4 (CH), 27.9 (3 x CH_3) and 22.3 (CH_3); *m/z* (EI) 211.121045 (M+, $C_{11}H_{17}NO_3$ requires 211.120844), 211 (M^+, 4 %), 196 (M^+-Me, 19), 155 (MH^+-^{t}Bu, 44), 140 (M^+-^{t}Bu-Me, 100) and 111 (MH^+-^{t}Bu-^{i}Pr).

Characterization of other compounds:

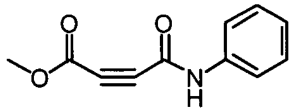
AC3



AC3

100%.; R_f 0.1 (hex/EA, 4:1); (Found C, 61.74; H, 4.87; N, 6.02; O, 27.51; $C_{12}H_{11}NO_4$ requires C, 61.80; H, 4.75;N, 6.01; O, 27.44); (retention time 3 minutes, 31 seconds); ^{1}H-NMR (400 MHz, $CDCl_3$) 8.47 (1H, br s), 7.45 (2H, d, *J* 12.5), 6.88 (2H, d, *J* 12.5), 3.86 (3H, s) and 3.80 (3H, s); ^{13}C-NMR (100 MHz, $CDCl_3$) 157.3 (C_q), 152.7 (C_q), 148.0 (C_q), 129.5 (C_q), 121.9 (CH), 114.3 (CH), 77.6 (C_q), 74.1 (C_q), 55.5 (CH_3), 53.5 (CH_3); *m/z* (EI) 233.069052 (M^+, $C_{12}H_{11}NO_4$ requires 233.068808), 233 (M^+, 7 %), 122 (15) and 62 (100).

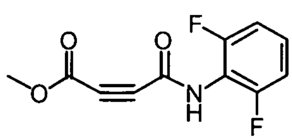
AC6



AC6

71 % yield; **R_f (hex/EA,)**; (retention time 3 minutes, 32 seconds); ^{1}H-NMR (400 MHz, $CDCl_3$) 7.59 (1H, br s), 7.51 (2H, d, *J* 7.7), 7.36-7.32 (2H, m), 7.18 (1H, m) and 3.86 (3H, s); **^{13}C-NMR (100 MHz, $CDCl_3$)**; *m/z* (EI) 203.058896 (M^+, $C_{11}H_9NO_3$ requires 203.058243), 203 (M^+, 64 %), 172 (M^+-OMe, 35) and 145 (MH^+-CO_2Me, 100).

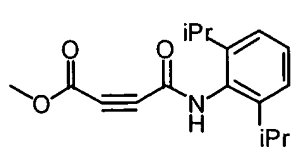
AC9



AC9

33 % yield**; R_f (hex/EA,);** (retention time 2 minutes, 58 seconds); **dodgy** ^{1}H-NMR (400 MHz, $CDCl_3$) 7.32-7.25 (2H, m), 7.08-6.97 (2H, m), 3.88 (3H, s) and 3.80 (1H, br s); ^{13}C-NMR (100 MHz, $CDCl_3$) get peak labels on spectrum; *m/z* (EI) 239.039140 (M^+, $C_{11}H_7F_2NO_3$ requires 239.039400), 239 (M^+, 100 %), 220 (M^+-F, 59) and 203 (M^+-OMe, 62).

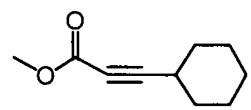
AC10



AC10

80 % yield; R_f 0.26 (hex/EA, 4:1); (Found C, 70.88; H, 7.22; N, 4.88; O, 16.49; $C_{17}H_{21}NO_3$ requires C, 71.06; H, 7.37; N, 4.87; O, 16.70); (retention time 2 minutes, 13 seconds);**dodgy**, **doris'** ^{1}H-NMR (300 MHz, $CDCl_3$) 7.22-7.20 (3H, m), 3.90 (3H, s), 3.05 (2H, m) and 1.17 (12H, 2 x d, *J* 7.0); ^{13}C-NMR (75 MHz, $CDCl_3$) 147.3 (C_q x 2), 146.3 (C_q x 2), 129.4 (C_q), 124.0 (CH x 3), 77.6 (C_q), 67.6 (C_q), 53.6 (CH_3), 29.0 (CH_3), 28.8 (CH_3) and 23.7 (CH); *m/z* (EI) 287.151570 (M^+, $C_{17}H_{21}NO_3$ requires 287.152144), 287 (M^+, 52 %), 255 (MH^+-OMe, 57), 240 (100) and 212 (92).

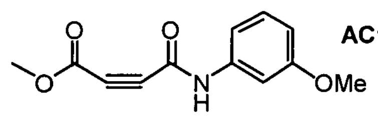
AC11



AC11

% yield; Rf (hex/EA,); (retention time minutes, seconds); ^{1}H-NMR (400 MHz, $CDCl_3$); ^{13}C-NMR (100 MHz, $CDCl_3$); *m/z* (EI) (M+, CHNO requires),.

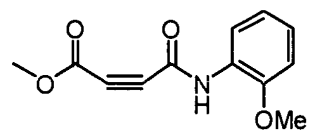
AC15



AC15

50% yield; R_f 0.1 (hex/EA, 4:1); (retention time 3 minutes, 31 seconds); ^{1}H-NMR (400 MHz, $CDCl_3$) 8.47 (1H, br s), 7.45 (2H, d, *J* 12.5), 6.88 (2H, d, *J* 12.5), 3.86 (3H, s) and 3.80 (3H, s); ^{13}C-NMR (100 MHz, $CDCl_3$) 157.3 (C_q), 152.7 (C_q), 148.0 (C_q), 129.5 (C_q), 121.9 (CH), 114.3 (CH), 77.6 (C_q), 74.1 (C_q), 55.5 (CH_3), 53.5 (CH_3); *m/z* (EI) 233.069052 (M^+, $C_{12}H_{11}NO_4$ requires 233.068808), 233 (M^+, 7 %), 122 (15) and 62 (100).

AC16

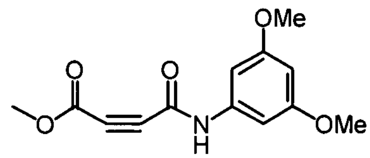


AC16

56 % yield; Rf 0.44 (hex/EA, 1:1); (retention time 3 minutes, 27 seconds); ^{1}H-NMR (400 MHz, $CDCl_3$) 8.28 (1H, dd, *J* 1.4, 8), 8.21 (1H, br s), 7.11 (1H, apparent dt, *J* 1.5, 7.7), 6.97 (1H, dt, *J* 0.9, 8.7), 6.90 (1H, d, *J* 8.2), 3.91 (3H, s) and 3.87 (3H, s); ^{13}C-NMR (100

MHz, $CDCl_3$) 153.2 (C_q), 148.1 (2 x C_q), 126.9 (C_q), 125.7 (CH), 121.5 (CH), 120.9 (CH), 110.5 (CH), 78.1 (C_q), 74.1 (C_q), 56.2 (CH_3) and 53.8 (CH_3); *m/z* (EI) 233.068297 (M^+, $C_{12}H_{11}NO_4$ requires 233.068808), 233 (M^+, 100 %), 218 (M^+-Me, 3), 202 (M^+-OMe, 25) and 175 (MH^+-CO_2Me, 40).

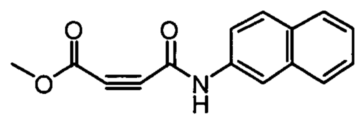
AC17



AC17

30% yield; Rf (hex/EA,); (retention time 3 minutes, 42 seconds); ^{1}H-NMR (500 MHz, $CDCl_3$) 7.69 (1H, br s), 6.73 (2H, s), 6.30 (1H, s), 3.86 (3H, s) and 3.79 (6H, s); ^{13}C-NMR (125 MHz, $CDCl_3$) 161.2 (2 x C_q), 152.6 (C_q), 148.1 (C_q), 138.2 (C_q), 95.5 (2 x CH), 97.9 (CH), 77.4 (C_q), 74.1 (C_q), 55.5 (2 x CH_3) and 53.5 (CH_3); *m/z* (EI) 263.079901 (M^+, $C_{13}H_{13}NO_5$ requires 263.079373), 263 (M^+, 31 %), 235 (45), 232 (M^+-OMe, 35), 204 (M^+-CO_2Me, 100).

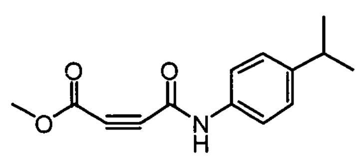
AC19



AC19

81% yield; R_f 0.14 (hex/EA, 4:1); (retention time 3 minutes, 26 seconds); ^{1}H-NMR (400 MHz, $CDCl_3$) 8.21 (1H, s), 7.95-7.79 (3H, m), 7.70 (1H, br s), 7.51-7.42 (3H, m) and 3.92 (3H, s); ^{13}C-NMR (100 MHz, $CDCl_3$) 153.2 (C_q), 148.8 (C_q), 134.5 (C_q), 133.9 (Cq), 131.5 (C_q), 129.5, 128.3, 128.0, 127.2, 126.2, 119.8 and 118.1 (7 x CH), 78.1 (C_q), 74.7 (C_q), 53.9 (CH_3); *m/z* (EI) 253.074299 (M^+, $C_{15}H_{11}NO_3$ requires 253.073893), 253 (M^+, 67 %), 222 (M^+-OMe, 22), 195 (MH^+-CO_2Me, 28), 115 (100).

AC20

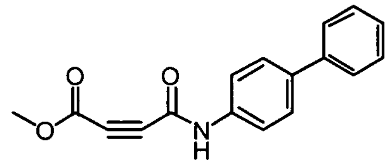


AC20

48% yield; R_f 0.11 (hex/EA, 4:1); (retention time 5 minutes, 53 seconds); ^{1}H-NMR (500 MHz, $CDCl_3$) 7.63 (1H, br s), 7.41 (2H, d, *J* 8.5), 7.19 (2H, d, *J* 8.5), 3.86 (3H, s), 2.93-2.86 (1H, m) and 1.23 (6H, d, *J* 4.5); ^{13}C-NMR (125 MHz, $CDCl_3$) 152.9 (C_q), 148.2

(C_q), 146.6 (C_q), 134.4 (C_q), 127.1 and 120.2 (4 x CH), 77.2 (C_q), 74.0 (C_q), 53.5 (CH_3), 33.7 (CH) and 23.9 (CH_3 x 2); *m/z* (EI) (M^+, CHNO requires).

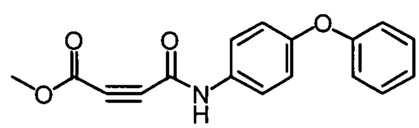
AC21



AC21

26% yield; R_f (hex/EA,); (Found C, 73.14; H, 4.85; N, 5.05;O, 17.00; $C_{17}H_{13}NO_3$ requires C, 73.11;H, 4.69;N, 5.01;O, 17.19); ^{1}H-NMR (500 MHz, $CDCl_3$) 7.67 (1H, br s), 7.59-7.55 (6H, m), 7.46-7.42 (2H, m), 7.37-7.33 (1H, m) and 3.88 (3H, s); ^{13}C-NMR (125 MHz, $CDCl_3$) 153.2 (C_q), 148.6 (C_q), 140.5 (C_q), 138.9 (C_q), 136.2 (C_q), 129.3, 128.2, 127.8, 127.3 and 120.9 (9 x CH), 77.9 (C_q), 74.7 (C_q) and 53.9 (CH_3); *m/z* (EI) 279.088946 (M^+, $C_{17}H_{13}NO_3$ requires 279.089543), 279 (M^+, 100 %), 193 (62), 168 (65) and 141 (70).

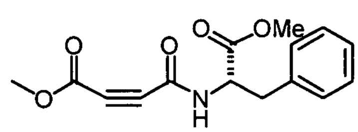
AC22



AC22

50% yield; R_f (hex/EA,); (Found C, 70.21; H, 4.32; N, 5.19; $C_{17}H_{13}NO_4$ requires C, 69.15; H, 4.44; N, 4.74; O, 21.67); (bad HPLC); ^{1}H-NMR (500 MHz, $CDCl_3$) 7.53 (1H, br s), 7.49 (2H, d, *J* 7.9), 7.35 (2H, app t, *J* 7.5), 7.11 (1H, app t, *J* 7.5), 7.0 (4H, d *J* 7.5) and 3.87 (3H, s); ^{13}C-NMR (125 MHz, $CDCl_3$) 157.0 (C_q), 154.7 (C_q), 152.7 (C_q), 148.2 (Cq), 131.8 (C_q), 129.9, 129.8, 123.5, 121.9, 119.4, 119.0 and 118.8 (9 x CH), 77.5 (C_q), 74.3 (C_q) and 53.5 (CH_3); *m/z* (EI) 295.084774 (M^+, $C_{17}H_{13}NO_4$ requires 295.084458).

AC23

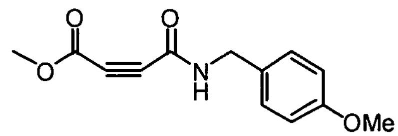


AC23

7% yield; Rf 0.15 (hex/EA, 4:1); (retention time 3 minutes, 27 seconds); ^{1}H-NMR (500 MHz, $CDCl_3$) 7.32-7.25 (3H, m), 7.09 (2H, d, *J* 8.2), 6.66 (1H, d, *J* 1.4), 4.90 (1H, app dt, *J* 5.7, 7.8), 3.81 (3H, s), 3.74 (3H, s), 3.19 (1H, dd, *J* 5.7, 18.7) and 3.11 (1H, dd, *J* 5.7, 14); ^{13}C-NMR (125 MHz, $CDCl_3$) 171.1 (C_q), 153.0 (C_q), 150.4 (C_q), 135.4 (C_q), 129.9,

129.6, 129.1, 128.0 and 127.8 (5 x CH), 77.7 (C_q), 74.5 (C_q), 57.5 (CH_3), 54.1 (CH_3), 53.1 (CH) and 37.9 (CH_2); *m/z* (EI) (M^+, CHNO requires).

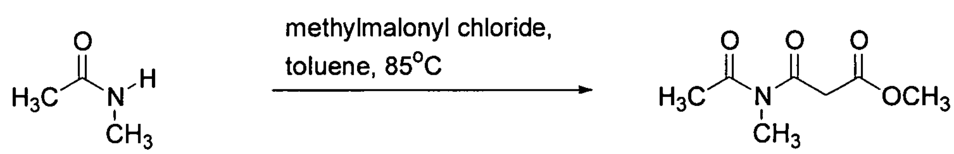
AC24



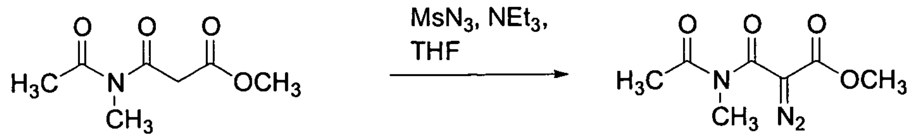
AC24

27% yield; R_f 0.44 (hex/EA, 1:1); (retention time 3 minutes, 26 seconds); ^{1}H-NMR (500 MHz, $CDCl_3$) 7.20 (2H, d, *J* 8.6), 6.88 (2H, d, *J* 8.6), 6.23 (1H, br s), 4.42 (2H, d, *J* 5.8), 3.81 (3H, s) and 3.80 (3H, s); ^{13}C-NMR (125 MHz, $CDCl_3$) 159.5 (C_q), 152.7 (C_q), 150.4 (C_q), 129.4 (CH x 2), 128.5 (C_q), 114.3 (2 x CH), 77.3 (C_q), 73.8 (C_q), 55.3 (CH_3), 53.3 (CH_3) and 43.7 (CH_2); *m/z* (EI) 247.084683 (M^+, $C_{13}H_{13}NO_4$ requires 247.084458), 247 (M^+, 56 %), 217 (MH^+-OMe, 40), 189 (MH^+-CO_2Me, 40), 136 (M^+-CO-tp-CO_2Me, 100), 121 ($OMePhCH_2^+$, 92).

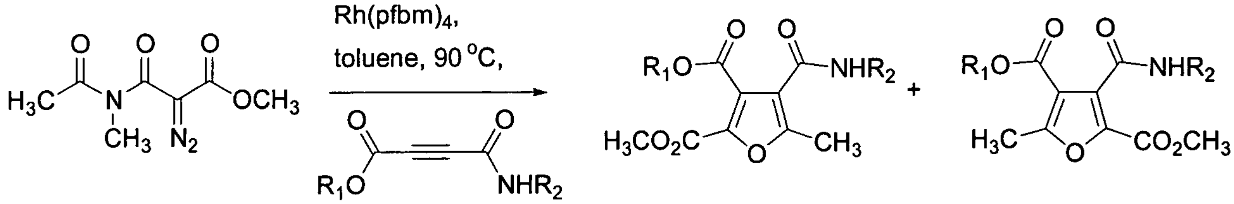
Preparation of the furan library (K1 and K2):



N-methylacetamide (1.00 g, 13.68 mmol) was dissolved in toluene (75 ml) and stirred at room temperature before methyl malonyl chloride (1.9 ml, 17.78 mmol) was added slowly. Nitrogen was bubbled through the reaction mixture, which was heated to 85 °C for 4 h. Upon cooling, diethyl ether (20 ml) was added and the reaction mixture was washed with sat. aq. sodium bicarbonate and sat. aq. sodium chloride solutions. The organic phase was dried with sodium sulfate, filtered and evaporated to dryness to afford a yellow liquid (1.72, 72%), which was used without further purification.

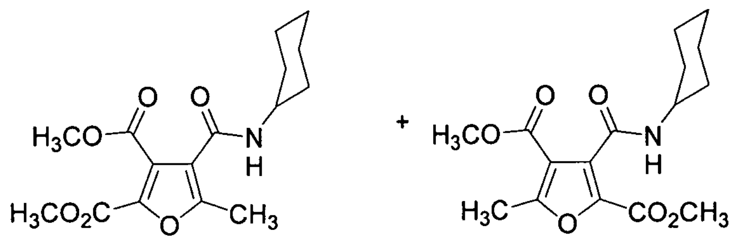


Triethylamine (2.1 ml, 15 mmol) was added to a solution of imide X (0.86 g, 5 mmol) in THF (20 ml) and methanesulfonyl azide (0.9 g, 7.5 mmol). The reaction mixture was left to stir at room temperature overnight before concentration *in vacuo*. Purifiaction by column chromatography (gradient elution from 10% to 40% EA/hex) gave a yellow oil (0.71 g, 71%).



The diazoimide (132 mg, 0.66 mmol) was combined with the acetylene (1.0 mmol) and rhodium perfluorobutyramidate (2.5 mg) in dry toluene (4 ml). The reaction mixture was allowed to stir at room temperature overnight then heated to 90 oC for 8 h. Evaporation of the solvent gave a yellow oil, which was purified by column chromatography (10% up to 50% EA/hex).

K1 and **K2**

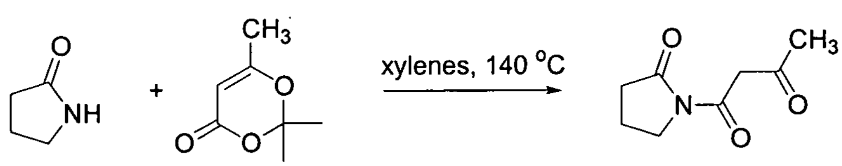


less polar 16% yield; R_f 0.52 (50% EA/hex); ^{1}H-NMR (300 MHz, $CDCl_3$) 7.04 (1H, br s), 3.94 (3H, s), 3.92 (3H, s), 3.88 (1H, m), 2.64 (3H, s), 1.94-1.92 (2H, m), 1.70-1.62 (3H, m), 1.44-1.31 (2H, m), 1.27-1.12 (3H, m); **^{13}C-NMR (75 MHz, $CDCl_3$) Doris' data.**

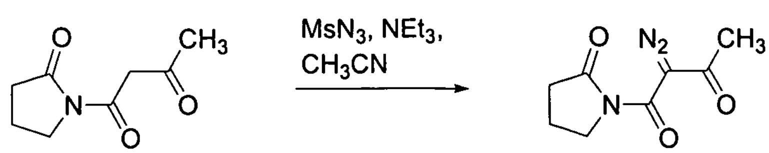
K2 (more polar)

39% yield; R_f 0.22 (50%EA/hex); ^{1}H-NMR (300 MHz, $CDCl_3$) 5.95 (1H, br s), 3.90 (3H, s), 3.88 (3H, s), 3.83 (1H, m), 2.64 (3H, s), 2.03-2.00 (2H, m), 1.76-1.71 (2H, m), 1.61 (1H, m), 1.43-1.36 (2H, m), 1.27-1.22 (3H, m); **^{13}C-NMR (75 MHz, $CDCl_3$) Doris' data.**

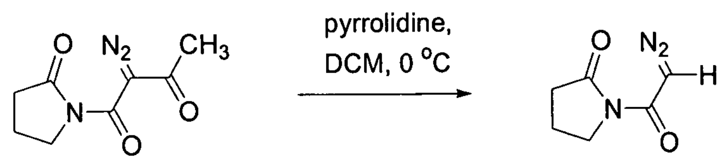
Preparation of the furan library with a 3-methylene unit at the 5-position



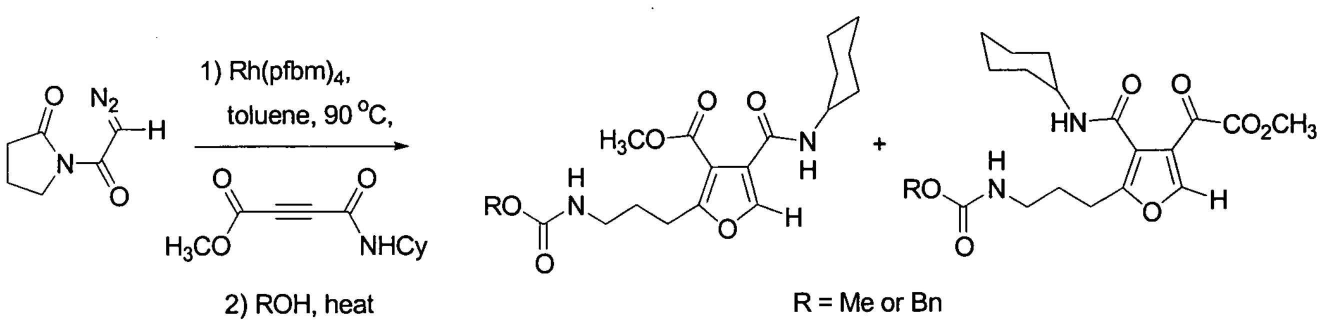
A solution contaning 2-pyrrolidinone (1.33 ml, 17.51 mmol) and 2,2,6-trimethyl-1,3-dioxen-4-one (2.75 ml, 21.1 mmol) in xylenes (17.5 ml) was heated to reflux under a nitrogen atmosphere for 2h. The solvent was removed under vacuum to give a brown oil, which was purified by column chromatography (5:1 hex/EA) affording the desired compound as a transparent oil that solidified in the freezer (2.82 g, 96%).



Triethylamine(3.0 ml, 21.3 mmol) was added to a solution of b-ketoimide (1.8 g, 10.6 mmol) and methanesulfonyl azide (1.55 g, 12.8 mmol) in acetonitrile (6 ml) at room temperature. The reaction mixture was stirred overnight and the solvent was removed under reduced pressure. The resulting residue was purified by column chromatography (20% EA/hex) to give 1.99 g (96%) of the desired product as a yellow oil.



Pyrrolidine (2.14ml, 25.64 mmol) was added dropwise to a solution containing the diazoimide (1g, 5.1 mmol) in dichloromethane (12 ml) at 0 oC under nitrogen atmosphere. The resulting solution was stirred at 0 oC for 2 h. before the solvent was removed under vacuum. The residue thereby obtained was purified by column chromatography (1:2 EA/hex) to give the desired product in 80% yield (632.4 g).

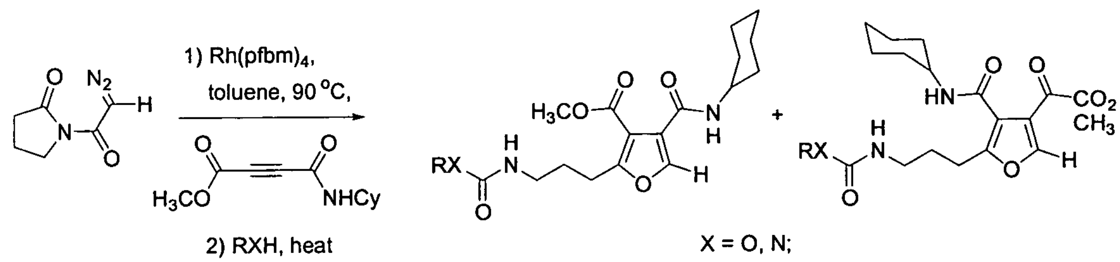


A solution of acetylene (168 mg, 0.80 mmol) and rhodium perfluorobutyramidate (cat) in toluene (1.5 ml) was heated to 95 oC under a nitrogen atmosphere. A solution of the diazoimide (112 mg, 0.73 mmol) in toluene (1.5 ml) was then added dropwise over 25 min. The solution was heated to reflux for 2 h. before it was cooled to room temperature and the solvent was evaporated under reduced pressure. The residue, typically yellow-brown was then dissolved in methanol (excess) and heated under reflux for 30 min. Upon

cooling, the alcohol evaporated *in vacuo* and its corresponding residue was purified by column chromatography to give a pale yellow oil.

Nucleophile = methanol: 13% yield;

Nucleophile = benzylalcohol : 26 % yield;



A solution of acetylene (168 mg, 0.80 mmol) and rhodium perfluorobutyramidate (cat) in toluene (1.5 ml) was heated to 95 oC under a nitrogen atmosphere. A solution of the diazoimide (112 mg, 0.73 mmol) in toluene (1s.5 ml) was then added dropwise over 25 min. The solution was heated to reflux for 2 h. before it was cooled to room temperature and a nucleophile (excess) and heated under reflux for 30 min. Upon cooling, the solvent evaporated *in vacuo* and its corresponding residue was purified by column chromatography to give a pale yellow oil.

Nucleophile = allylamine; 23% yield;

Nucleophile = 2-ethyl-1-butanol; 13 % yield;

Nucleophile = 1-butanol; 19% yield;

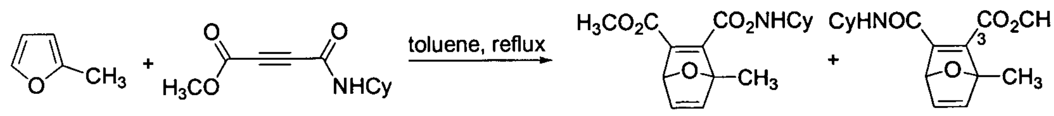
Nucleophile = *N*-Boc L-valinol; 14% yield;

Nucleophile = cyclohexanol; 16 % yield;

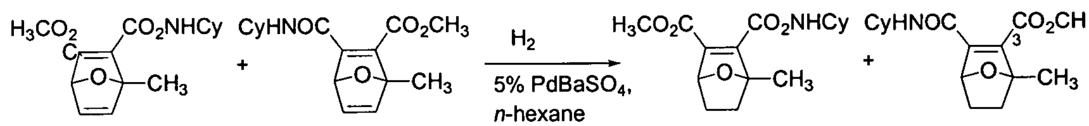
Nucleophile = *N*-Boc L-phenylalaninol; % yield;

Nucleophile = allylalcohol;

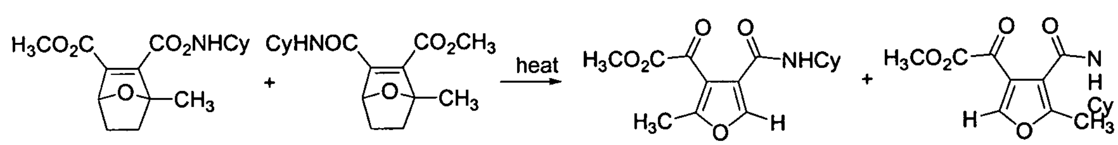
AN7A and **AN7B**



2-Methylfuran (0.5 ml, 5.49 mmol) was added to a solution of the acetylene (1g, 4.77 mmol) in toluene (5 ml) and the resulting solution was heated to reflux for 3h before the solvent was evaporated under vacuum. The resulting residue was purified by column chromatography (40% EA/hex) to give the product as a yellow oil (1.1 g, 80%).

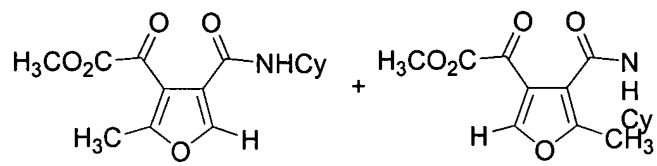


The mixture of regioisomers (700 mg, 2.4 mmol) in n-hexane (7 ml) was added to a stirred suspension of $PdBaSO_4$ (cat) in n-hexane. The mixture was degassed extensively and placed under hydrogen atmosphere at 0 oC. The reaction was followed closely by analysis of aliquots. After 30 min, the reaction was complete and the mixture was filtered through a pad of celite® and evaporated to give the desired compound as a transparent oil (700 mg, quant.).



The mixture of regioisomers was heated to give, after column chromatography purification (5% to 20% EA/hex), the two expected furans. The less polar furan was obtained in 20%, the most polar furan in 32% and a mixture of both in 25%.The furans could be further purified by HPLC (80% MeOH/H2O, C18 column).

AN7A and AN7B



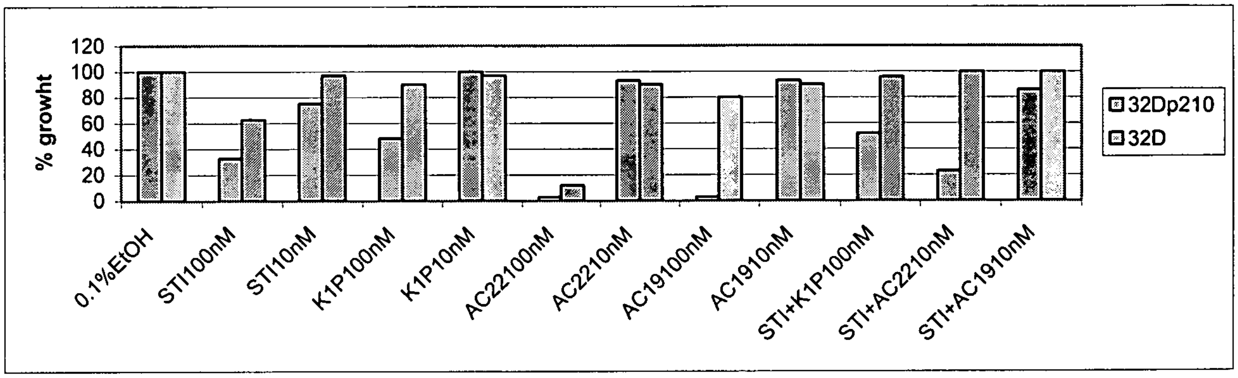
less polar: R_f 0.5 (hex/EA 3:2); (Found C, 63.17; H, 7.23; N, 5.24; $C_{14}H_{19}NO_4$ requires C, 63.38; H, 7.22; N, 5.28); (retention time 7 minutes, 27 seconds); ^{1}H-NMR (400 MHz, $CDCl_3$) 9.23 (1H, br s,), 7.90 (1H, s), 3.94-3.89 (1H, m), 3.87 (3H, s), 2.68 (3H, s), 1.99-1.96 (2H, m), 1.77-1.73 (2H, m), 1.55-1.54 (1H, m) and 1.43-1.31 (5H, m); **^{13}C-NMR (100 MHz, $CDCl_3$); *m/z* (EI);** more polar R_f 0.4 (hex/EA 3:2); (Found C, 63.45; H, 7.24; N, 5.27; $C_{14}H_{19}NO_4$ requires C, 63.38; H, 7.22; N, 5.28); (retention time 6 minutes, 14 seconds); ^{1}H-NMR (400 MHz, $CDCl_3$) 9.22 (1H, br s,), 7.95 (1H, s), 3.96-3.92 (1H, m), 3.90 (3H, s), 2.57 (3H, s), 1.99-1.95 (2H, m), 1.76-1.72 (2H, m), 1.58 (1H, m) and 1.43-1.31 (5H, m); **^{13}C-NMR (100 MHz, $CDCl_3$) ; *m/z* (EI)**

Biological Testing

A number of compounds according to the present invention were tested for activity using the following three systems: a low cell density high throughput cell proliferation assay, a high cell density proliferation assay and a cell free kinase inhibition assay as described below. Activity was exhibited with several compounds according to the present invention consistent with these compounds being used in the treatment of tumors, cancer and other cell growth proliferation assays.

<u>Low cell density high throughput cell proliferation assay</u> Between 50 and 100 32D and 32DtetP210Bcr-Abl cells in 100 microliters of medium without serum were exposed to the test compound for 15 minutes. An equal volume of 20% serum supplemented tissue culture medium was then added and the cells were inoculated in single well in 32 wells of a 96 well plate. The endpoint of the assay was the fraction of the 32 wells in which a cell

pellet was seen to develop which was filled with live cells. This assay is subject to automated screening by a plate reader for the cell pellet. We used this high throughput assay to screen for compounds that suppress the growth of the 32DtetP210Bcr-Abl cell line in the absence of IL-3, but allow the growth of the 32D cell line in the presence of IL-3. Various concentrations of each compound were tested. If a compound suppressed the growth of the P210Bcr-Abl cell line without affecting the growth of the 32D cell line, then the compound was considered to be selectively inhibitory for the P210Bcr-Abl dependent growth.

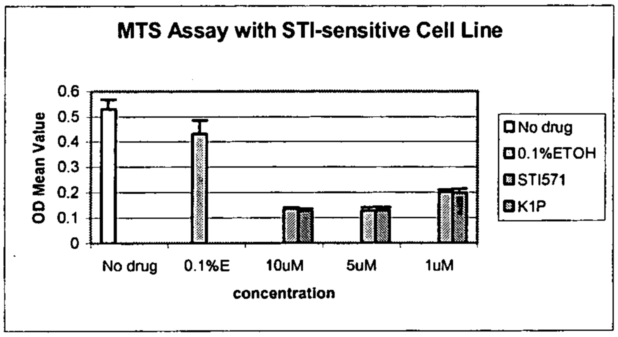


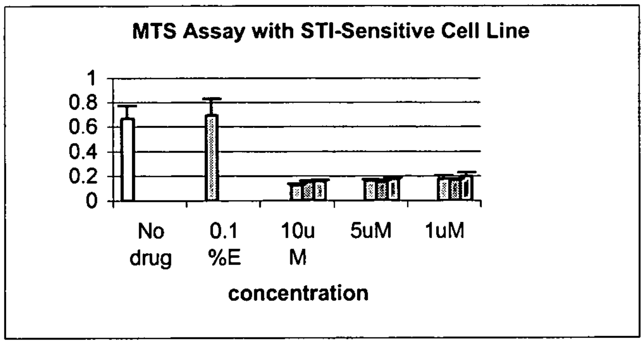
As shown above, the compounds derived from the linear acetylene compounds, AC22 and K1P, are inhibitory to the 32DtetP210bcrabl cell line at 1 micromolar. AC22 also inhibits the 32Dtet cell line at a similar concentration. The effect of these compounds were also studied in combination with Imatinib (Gleevec or STI-571) to determine whether the compound had an additive or synergistic effect with Imatinib in inhibiting P210bcrabl dependent cell growth. As shown above, the inhibition of the combination of AC19 and Imatinib (STI571) at a concentration of 10 nanomolar of each drug (15% inhibition) is less than the sum of the inhibitory effect of both drugs alone (25%). When compound AC22 or K1P are added in combination with Imatinib to the culture of the 32DtetP210bcrabl cell line at 10 nanomolar concentration of both drugs, there is inhibition of the growth of the P210bcrabl dependent proliferation (80%) This is greater than the sum of the inhibition that is seen when the drugs (Imatinib inhibits 25% and AC22 inhibits 10%) are used separately. A similar synergism is seen for K1P and AC19: 45% inhibition together and 25% when used alone.

High cell density cell proliferation assay (MTS)

This cell proliferation assay was performed using MTS tetrazolium (Cell titer96 Aqueous; Promega, Madison, WI), which measure numbers of viable cells. Between $2x10^3$ and $2x10^4$ STI-resistant cells are washed twice in RF-10 and plated in quadruplicate in the wells of a microtiter plate in 100µl of RF-10 medium supplemented with various doses of test compounds. Controls using the same concentration of Imatinib without cells were set up in parallel. The plate is then incubated for 72 hours at 37 C in a humidified 5% CO2 atmosphere. Twenty microliters of MTS were then added to the wells and the plate was incubated for three hours. Then the absorbance was recorded at 490-nm wavelength with a microplate autoreader (Spectramax). Results are expressed as the mean optical density of the 4-well set of each compound dose. All experiments were repeated at least 3 times.

Compounds identified as being selectively inhibitor for P210BcrAbl growth in the low density assay were also tested in a high cell density assay in which the number of cells was closer to that present in the blood stream in the presence of serum. This high cell density assay was not used to screen drugs initially but was used for in depth studies of compounds that were selected on the basis of the low cell density assay.





Cell Free Kinase Inhibition Assay. A panel of 60 kinases (Upstate Biotechnologies, Lake Placid, NY) were analyzed in in vitro cell free kinase assays. The results for those kinases with associated inhibition are shown below.

Kinase	% Inhibition at 10 μM*	
	K1P	AC22
CaMKII	-	40
CaMKIV	-	64
CDK2/cyclinA	-	50
CK1	46	(37)
Fyn	49	(29)
IKKBeta	-	45
Lyn	-	98
PKCy	-	61
PKCbII	(35)	48

*only % of inhibition >45% is reported

Testing of Compounds According to the Present Invention by NCI

The following cells lines were used to test the activity of compounds according to the present invention.

Cell Line Name	Panel Name	Cell Number	Panel Number	Inoculation Density
CCRF-CEM	Leukemia	3	7	40000
HL-60(TB)	Leukemia	8	7	15000
K-562	Leukemia	5	7	5000
MOLT-4	Leukemia	6	7	30000
RPMI-8226	Leukemia	10	7	30000
SR	Leukemia	19	7	20000
A549/ATCC	Non-Small Cell Lung Cancer	4	1	7500
EKVX	Non-Small Cell Lung Cancer	8	1	20000
HOP-18	Non-Small Cell Lung Cancer	27	1	20000
HOP-19	Non-Small Cell Lung Cancer	28	1	20000
HOP-62	Non-Small Cell Lung Cancer	26	1	10000
HOP-92	Non-Small Cell Lung Cancer	29	1	20000
NCI-H226	Non-Small Cell Lung Cancer	13	1	20000
NCI-H23	Non-Small Cell Lung Cancer	1	1	20000
NCI-H322M	Non-Small Cell Lung Cancer	17	1	20000
NCI-H460	Non-Small Cell Lung Cancer	21	1	7500
NCI-H522	Non-Small Cell Lung Cancer	3	1	15000
LXFL 529	Non-Small Cell Lung Cancer	30	1	10000
DMS114	Small Cell Lung Cancer	9	2	20000
DMS 273	Small Cell Lung Cancer	11	2	5000
SHP-77	Small Cell Lung Cancer	13	2	40000
COLO 205	Colon Cancer	10	4	15000
DLD-1	Colon Cancer	11	4	5000
HCC-2998	Colon Cancer	2	4	10000
HCT-116	Colon Cancer	3	4	5000
HCT-15	Colon Cancer	15	4	10000
HT29	Colon Cancer	1	4	5000
KM12	Colon Cancer	17	4	15000
KM20L2	Colon Cancer	18	4	10000
SW-620	Colon Cancer	9	4	10000
SF-268	CNS Cancer	14	12	15000

Cell Line Name	Panel Name	Cell Number	Panel Number	Inoculation Density
SF-295	CNS Cancer	15	12	10000
SF-539	CNS Cancer	16	12	15000
SNB-19	CNS Cancer	2	12	15000
SNB-75	CNS Cancer	5	12	20000
SNB-78	CNS Cancer	6	12	20000
TE671	CNSCancer	10	12	20000
U251	CNS Cancer	9	12	7500
XF 498	CNS Cancer	17	12	20000
LOX IMVI	Melanoma	1	10	7500
MALME-3M	Melanoma	2	10	20000
M14	Melanoma	14	10	15000
RPMI-7951	Melanoma	3	10	20000
M19-MEL	Melanoma	16	10	10000
SK-MEL-2	Melanoma	5	10	20000
SK-MEL-28	Melanoma	8	10	10000
SK-MEL-5	Melanoma	7	10	10000
UACC-257	Melanoma	21	10	20000
UACC-62	Melanoma	20	10	10000
IGROV1	Ovarian Cancer	10	6	10000
OVCAR-3	Ovarian Cancer	1	6	10000
OVCAR-4	Ovarian Cancer	2	6	15000
OVCAR-5	Ovarian Cancer	3	6	20000
OVCAR-8	Ovarian Cancer	5	6	10000
SK-OV-3	Ovarian Cancer	11	6	20000
786-0	Renal Cancer	18	9	5000
A498	Renal Cancer	13	9	20000
ACHN	Renal Cancer	23	9	10000
CAKI-1	Renal Cancer	15	9	10000
RXF 393	Renal Cancer	16	9	15000
RXF-631	Renal Cancer	17	9	10000
SN12C	Renal Cancer	8	9	15000
SN12K1	Renal Cancer	10	9	10000
TK-10	Renal Cancer	24	9	15000
UO-31	Renal Cancer	4	9	15000
P388	Leukemia	1	7	5000
P388/ADR	Leukemia	2	7	5000
PC-3	Prostate Cancer	1	11	7500
DU-145	Prostate Cancer	3	11	10000
MCF7	Breast Cancer	1	5	5000
NCI/ADR-RES	Breast Cancer	2	5	15000
MDA-MB-231/ATCC	Breast Cancer	5	5	20000
HS 578T	Breast Cancer	6	5	20000
MDA-MB-435	Breast Cancer	11	5	15000

Cell Line Name	Panel Name	Cell Number	Panel Number	Inoculation Density
MDA-N	Breast Cancer	12	5	15000
BT-549	Breast Cancer	13	5	20000
T-47D	Breast Cancer	14	5	20000
MAXF 401	Breast Cancer	16	5	20000
MDA-MB-468	Breast Cancer	18	5	20000
SK-BR-3	Breast Cancer	10	5	20000

Results showed that the compound KIP exhibited enhanced activity against certain leukemia cell lines, colon cancer cell lines, melanoma cell lines, renal cancer cell lines and a breast cancer cell line, thus showing the potential for broad activity of the compound K1P as well as other compounds according to the present invention.

While the invention has been described with reference to specific methods and embodiments, it will be appreciated that various modifications may be made without departing from the invention.